March 7, 1974

Dr. William Pomerance
National Cancer Institute
9000 Rockville Pike
Bethesda, Maryland 20010

Re.: NCI Contract Application
RFP No. NCI-CB-74-29

Dear Dr. Pomerance,

This is to elaborate on the approach that we intend to follow, under the reference research project, in characterizing controls for our search for biochemical markers for cancer risk and incidence. We have already collected a substantial number of specimens from "normal healthy individuals" which examined in the aggregate, as well as by the pooling of considerable samples, give us an initial base-line of expectation of "normal metabolites". These would be substances whose prevalance is already so high that regardless of their possible role in pathogenesis would be unlikely candidates for providing diagnostically useful signatures.

Already in Dr. Fair's collection from his urological service are a substantial number of frozen urine samples reflecting specimens from patients showing a variety of pathologies or as insidental part of other work-ups with no evident pathology in the final outcome. In the event that a provocative signature appears these samples would then be scanned for the presence of the indicated substance to give a preliminary idea of its distribution.

We do not intend at this time to initiate a prospective study which has been pre-programmed in detail with respect to the identified variables, feeling that this would be a costly enterprise with an inadequate theoretical base. Instead if our exploratory work turns up candidate substances, we will attempt to elaborate specific mechanistic hypotheses to account for their origin — for example as byproducts of drugs, of specific dietary inputs, of disturbances in normal intermediary metabolism, or as special products associated with cellular proliferation and degredation. In the context of these specific findings and specific hypotheses we will then attempt to specify the most cogent and probable variables that would relate to a concrete theoretical framework. We believe, however, that many extraneous variables — for example diet — can most readily be examined by comparisons of members from the same household.

This research design can be sharpened by contrasts between genetically related individuals, on the on hand, and genetically unrelated spouses on the other. This is important to emphasize since some of the most interesting markers may be concerned with genetic predisposition to cancer rather than to the actual development of neoplastic disease. However, we believe it would be unrealistic to outline detailed protocols for epidemiological examination until we had more clearly delineated the nature of the substances likely to be of the greatest interest and had formulated some biochemical-mechanistic-hypotheses of their role. In our original presentation, however, we did indicate a list of variables that we believe must be attended to with circumspection in any surveys of this kind in order to avoid some of the fiascos that have attended efforts at identifying biochemical stigmata of psychiatric disease.

Fortunately, from the standpoint of this kind of investigation we operate in an active clinical care setting and could therefore have ready access to large numbers of urine samples from a very broad variety of patient sources. In addition, it would be easy to obtain volunteers from the nearby student and faculty population including some pre-selection for the general variables previously indicated (sex, age, recent health status, usage of tobacco, alcohol, and prescribed drugs, etc.). In addition, our continuing studies on newborns, and their families for the detection of new forms of genetic disease gives us convenient and inexpensive access to additional potential control populations.

Sincerely yours,

Joshua Lederberg
Professor of Genetics

JL/rr